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OUR REF: PB - 46676

YOUR REF:

30th March, 2004

The International Preliminary Examining Authority,
The European Patent Office,
Erhardstrasse 27,
D-8000 Munchen 2,
Germany

Dear Sirs,

Re: International Patent Application No. PCT/GB03/03654
PHOQUS PHARMACEUTICALS LIMITED

We refer to the Written Opinion dated 19th March, 2004 and would make the following observations.

The subject invention is concerned with a method of making tablets, to the tablets themselves and to compositions for making tablets. In particular, the invention is directed to the problem encountered when citric acid is used in an aqueous solution as the granulating liquid for the preparation of tablet granules. It has been found that when such granules are used to prepare tablets significant difficulties are encountered due to extensive sticking of the material during compression of the granules to form the tablet.

In the past, lubricants or anti-adherent have been added to the granulation mixture in an attempt to avoid the problem of sticking. The sticking problem associated with using citric acid solution as a granulation liquid cannot be resolved even with using increasing amounts of conventional lubricants and anti-adherents.

The subject invention solves this problem by the incorporation of a highly water-soluble sugar in the aqueous solution of citric acid which is used as a binder for granulation.

Claim 1 is directed to the use of an aqueous solution of citric acid and a highly water-soluble sugar as a binder for the granulation of tablet excipients.

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Claim 8 is directed towards a composition for compressing tablets comprising granules of tablet excipients in which the granules comprise citric acid and highly water-soluble sugar as binder.

Claim 15 is directed towards a tablet comprising granules of tablet excipients in which the granules comprise citric acid and highly water-soluble sugar as binder.

Claim 22 is directed towards a method of making a tablet which comprises the step of granulating tablet excipients using an aqueous solution of citric acid and a highly water-soluble sugar as a binder and thereafter compressing the dried granules into a tablet.

The Applicants respectfully submit that all claims are novel and inventive over the state of the art.

With regard to WO03/072084, this document is not a prior publication and it is only necessary for the claims of the subject application to be novel over any disclosure in the reference which is entitled to an earlier priority date than the respective claim. Although Examples 7, 8 and 9 of WO03/072084 are formulations which disclose the subject invention, those Examples are entitled to a priority date of 28th February, 2003 since those Examples were introduced on the International filing date. The claims of the subject application are identical to those on British Patent Application No. 0219744.0 and are therefore entitled to the priority date of 23rd August, 2002. Thus, this reference may be disregarded.

EP 1116485 was cited by the search examiner as being particularly relevant to Claims 1 to 4. The examiner relied upon Example 1 of the reference. This reference discloses pharmaceutical formulations in the form of instant granules and processes for the preparation thereof. While it is accepted that the Examples use solutions of sugar and citric acid in a granulation process, the granules are not used as tablet excipients. There is no disclosure that the resulting granules are formed into tablets and no disclosure or hint that the resulting granules would be suitable for use in making tablets. Thus, the disclosure of this reference does not anticipate any of the claims.

The objective of EP 1116485 was to improve the formulation described in EP 232277 and its preparation in such a way that instant granules and a process for their preparation are provided, by means of which it is possible to easily accommodate very large amounts of even different, in particular insoluble or slightly soluble, active substances etc. After introduction into water, the pharmaceutical formulation should be suspended within an appropriately short time by stirring and should have a pleasant taste and should furthermore remain in suspension for an appropriately long time. Thus, the subject matter of this reference is directed to a completely different problem to the subject invention and the pharmaceutical formulations of the reference, which are in the form of instant granules. The properties required for such products are totally different from the properties required for tablet production and this reference would not be regarded as a likely starting point to solve the problem of sticking during the production of tablets by compression. There is no indication whatsoever in the reference that the products

would solve the problem of sticking during compression into tablets. Thus, the Applicants submit that this reference does not render any of the claims obvious.

In view of the fact that the final date by which the International preliminary examination report must be established is 12th December, 2004, the Applicants would be grateful if the examiner would issue a further Written Opinion in the event he is not inclined to issue a totally favourable International preliminary examination report.

Yours faithfully,

P.A. BOWMAN
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